A CLINICAL STUDY OF THE COAGULATION TIME OF BLOOD.

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We have felt for some time the need of a clinical method for determining the coagulation time of the blood which would be more satisfactory than the numerous methods previously used. The various ones which we have tried have proved unreliable in our hands. Cohen,[1] in a very complete paper on the "Coagulation Time," has discussed thirty-one methods and their modifications, and we would refer for full bibliography to his paper. Nearly all these methods fail to recognize what physiologists[2] have demonstrated long ago—namely, that contact with tissue markedly accelerates the coagulation time of the blood.

It is not our purpose to touch upon the various theoretic considerations of the coagulation of the blood or constituents of the blood necessary to coagulation, but mention must be made of the valuable work of Howell,[3] whose theory of the coagulation of blood seems to satisfy all requirements.

Pratt,[4] in 1903, writing from the Medical Clinic of Tübingen, embodied experimentally one of the chief principles of our method, although he used the Pratt-Grützner coagulometer. He speaks of finding the coagulation time of blood taken directly from the arm vein of man to average from six to seven minutes normally. He writes as follows in regard to it: "Coagulation time can be determined with a fair degree of accuracy by this method, but as it involves the withdrawal of the blood, directly from the veins, it was not considered feasible." At the present day, when paracentesis of the veins is done so commonly and easily, it is no longer a difficult or dangerous procedure.

Morawitz and Bierich,[5] in 1907, published from Krehl's clinic a method of determining coagulation time in cholemic cases which closely resembles our own. Ten c.c. of blood were taken from an arm vein, 5 c.c. of this were put into test-tubes, which were watched for coagulation, and the remaining 5 c.c. were used for special examination of blood elements. Their series were apparently limited to the cholemic cases and their method was not generally adopted.

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[1] Archives of Internal Medicine, 1911, viii, 684.

[2] Howell, W. H., Text-book of Physiology, 1905, p. 418.

[3] Loc. cit.

[4] Jour. Med. Research, 1903, No. 1, x, 120.

[5] Arch. f. experiment. Pathologie und Pharmakologie, 1907, lvi, 115.

Addis,[6] in 1910, wrote of using a method of studying the coagulation time in hemophilia similar to that of Morawitz and Bierich, except that 2½ c.c. instead of 5 c.c. of blood were used for the test. Inversion of the tubes into which the blood was put showed the end-point.

Holmgren,[7] in 1912, found that Schultz's method of using blood obtained by skin puncture was unsatisfactory, and therefore recommends venous puncture for obtaining blood for determination of coagulation time by a special coagulometer.

Dochez,[8] at the Rockefeller Institute, has been using during the period of our study a method similar to ours, but more accurate and correspondingly less practical clinically. In a series of cases of pneumonia, acute and convalescent, Dochez has determined the coagulation time by withdrawing about 7 c.c. of blood from an arm vein into a syringe, emptying this blood into a carefully prepared test-tube, and then watching for the end-point by tilting the tube every thirty seconds. The test-tube is kept at 37° C.

Thus although the method to be described is not completely new, it has been used on so small a scale and in such limited series as to justify a more extended study.

Method. One c.c. of blood is withdrawn from an arm vein, using a small all glass syringe (for example, Burroughs and Wellcome, 20 minims), preferably with a platinum needle, the syringe having been first sterilized and rinsed out with normal salt solution. The time at which the blood is withdrawn is noted as accurately as possible; the needle is removed and the syringe is then emptied into a small glass tube (Widal tube), about 8 mm. in diameter, which has previously been rinsed out in normal salt solution. The tube is rotated endwise every thirty seconds, and that point at which the blood no longer flows from its position but maintains its surface contour when inverted is taken as the end-point. Care must be used to exclude air bubbles, as they tend to accelerate coagulation.

Observations as to the nature of the clot and of the time and extent of its retraction have been included as an important part of the method. We have controlled nearly all our cases with the coagulation time by Hayem's[9] method, blood being obtained by a puncture of the ear with a mechanical lancet of uniform length (5 mm.). The blood used was also collected in a Widal tube as quickly as possible, and in as nearly uniform bulk as possible (that is 1 c.c.). It usually required more than one-half minute to collect this amount even after deep puncture. Our comparative results have shown the unreliability of the ear method. For example, a case of hemophilia gave a coagulation time of fifty minutes by the arm-vein method, but blood from the ear clotted in five minutes. The blood coagulated by this method (of Hayem) very uniformly between two and five minutes, with only four exceptions—namely, purpura hæmorrhagica, family type of Hanot's cirrhosis, gallstones, with marked jaundice and hemophilia. The longest time was twelve and one-half minutes in one case of hemophilia. In all four of these cases the coagulation time by the arm-vein method was also prolonged. Our only conclusion is that if the coagulation by using the blood from the ear is over five minutes, one would also find the coagulation time by using the arm vein prolonged, but negative results are of no value.

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[6] Quarterly Jour. Med., iv, 16; Jour. Path. and Bact., 1911, xv, 427.

[7] Münch. med. Woch., October 15, 1912, No. 42, p. 2281.

[8] Jour. Exper. Med., xvi, No. 5, p. 693.

[9] Paris, 1889, p. 323.

The advantages of the arm-vein method over those ordinarily used are briefly as follows: Blood is obtained directly from the blood stream without contact with tissue or skin, which contact must enter in as a factor of varying importance in the coagulation time of blood taken by skin punctures, as has been the procedure in nearly all previous methods. It has often been found that blood flowing freely from deep punctures clots much more slowly than blood expressed from shallow punctures, apparently because of the varying proportions of blood and tissue juice.[10] It is obviously difficult to make punctures every time of equal depth and in tissue of equal vascularity. Therefore the results are not strictly comparable.

Another important advantage over some of the methods described previously is the simplicity of our method, the coagulometer consisting merely of the syringe and the Widal tubes. Moreover, the end-point is usually quite definite and the element of personal equation is less than in most other methods.

After the coagulation time has been determined we still have a considerable clot to study as to its character, color, and retraction, which can hardly enter into the methods where but one or two drops are studied.

The disadvantages are as follows: One is the ratio of the amount of foreign surface to the bulk of blood. This ratio is quite large in our method, but the glass syringe and tube are as smooth and clean as possible and coated with normal salt solution. We consider that much of this disadvantage is obviated. Moreoever, the fact that like all methods this method is not absolute but only relative, practically rules out the argument of surface and volume ratio.

The discomfort to the patient of puncture of a vein for the blood is slight, as a rule, and has been no more disagreeable than the ear puncture. Moreover the blood may often be obtained for the test at the same time that blood is being taken for a blood culture, Wassermann, or other tests, a larger syringe being used, and a slight error thus introduced.

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[10] Howell, W. H., Amer. Jour. Physiol., October 1, 1912; Text-book on Physiology, 1905, p. 418.

Temperature has an important bearing on the coagulation time, as has already been indicated by Addis,[11] Wright,[12] Brodie and Russell,[13] Cohen,[14] Morawitz and Lissen,[15] and others.

We have studied the coagulation time in 3 cases—2 normal and 1 with gastric ulcer—at varying degrees of temperature, using water baths to maintain the temperature about the Widal tubes. The results are shown by the three curves (Fig. 1).

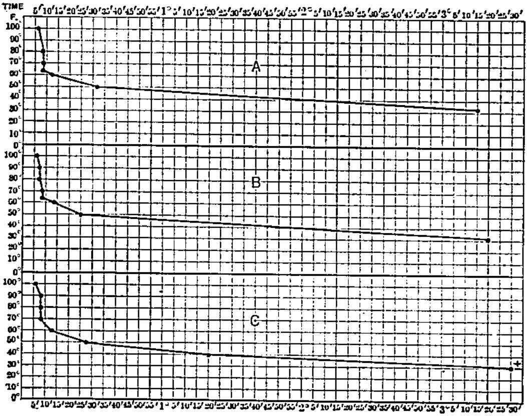

FIG. 1.—Relation of temperature and coagulation. *A*, healthy case; *B*, crse of peptic ulcer; *C*, healthy case.

These curves indicate that if the test is done at a room temperature of 65° to 90° F., the error, although present, is within one minute, and may be neglected. However, if the temperature is below 65° or above 90° F., a warm or cool water bath should be used, maintaining a temperature of 70° F. as mean. The tests of coagulation time which we have done in summer and autumn have been in a ward with a temperature range of 65° to 90° F. The addition of an incubator, as in Dochez' method, between the degrees of 65° and 90° F. would detract from the practicability more than it would add to the accuracy.

Hinman and Sladen,[16] in 1907, showed that the coagulation time of blood from the same person varied considerably with the time of day. In a case tried by our method we found little or no variation in the coagulation time of blood taken morning, afternoon, and evening. At 8.45 A.M., just after breakfast, the time was eight minutes; at 12 M., just before dinner, it was eight minutes; at 4.15 P.M. (before supper) it was seven and one-half minutes, and at 7.30 P.M. it was eight minutes. Thus at times during the day when coagulation would ordinarily be tested our method shows sufficient uniformity.

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[11] Quarterly Jour. Exper. Phys., 1908, i, 305.

[12] British Med. Jour., 1894, i, 237.

[13] Jour. Phys., London, 1817, xxi, 403; K. Burker, Pflüger's Archiv, 1904, cii, 36.

[14] Loc. cit.

[15] Deut. Arch. f. klin. Med., 1908, xciv, 110.

[16] Bull. Johns Hopkins Hosp., xviii, 207.

The results of observations of the coagulation time with the method just described on 125 cases of all kinds are shown in the accompanying table.

TABLE OF COAGULATION TIMES.

Disease.	No. of cases.	Average, arm vein.	Average, ear.	Limits, arm vein.	Limits, ear.
Normal	24	6½	3	5 - 8	2 - 4
Pernicious anemia	12	10⅔	3+	5 -15	2 - 4½
Secondary anemia from gastric ulcer	4	8	3½	5 -14	2 - 5
hemorrhage	..	....	......	4 - 8	
Chlorosis	2	6			
Polycythemia	1	6	3		
Splenic anemia	1	15	3¾		
Myelogenous leukemia	3	6	3½	3 -10	3 - 4½
Lymphatic leukemia	1	10	3½		
Purpura hæmorrhagica	1	12½	6½	10 -15	4 - 9
Hemophilia	2	52½	12½	55 -50	5 -20
Diabetes (one with acidosis)	3	5-	3	3½- 7	2 - 3
Catarrhal jaundice	3	8 (–)	3 (–)	7 - 8½	2½- 3
Cancer of liver with jaundice	4	5¼ (–)	4	5 - 6½	2½- 4
Cancer of liver without jaundice	2	8	3¼	7 - 9	3 - 3½
Gallstones with marked jaundice	2	11¾	4½	8 -15½	3½- 5½
Syphilis of liver with jaundice	1	9	3¼		
Syphilis of liver without jaundice	1	7	3		
Atrophic cirrhosis with jaundice	1	10	2		
Atrophic cirrhosis without jaundice	2	4¾	2¼	4 - 5½	2 - 2½
Hypertrophic cirrhosis with jaundice	2	14½	7	12 -17	5 - 9
Hypertrophic cirrhosis, with jaundice, family type, toxic	1	6	2½		
Infections:					
Pneumonia	6	15½	4	6½-35	3½- 4½
Typhoid	16	7+	2¾	2½-15	1½- 4½
Streptococcic septicemia with arthritis, endocarditis, and pericarditis	1	11½	—	—	
Staphylococcus aureus, septicemia, and pyemia,	1	13	—	—	
Brill's disease	1	2¼	1¾	—	
Acute infection	5	6	3	4 -10½	2½- 4
Gonorrheal arthritis	1	5½	—	—	—
Endocarditis	4	6½	2½	2½-11½	1½- 3
Tænia	1	5	2¾	—	
Trichiniasis	1	10½	—	—	
Cardiorenals and cardiac decompensation	6	5¾	3½	4½- 6½	3¾- 5
Aortic disease	3	4½	3	4 - 5	2½- 3½
Nephritis with edema	3	9+	3	5½-14	3 .
Gastric ulcer (bleeding) with anemia	4	8	3⅔	5 -14	
Gastric ulcer (bleeding) without anemia	1	8	—	8	
Hyperthyroidism	1	7	2½	—	
Hemoptysis in tuberculosis	2	6¾	3½	8 - 5½	

Discussion of results in clinical cases:

Normal Coagulation Time. We have found the *normal* coagulation time of blood taken by this method to be six and one-half minutes as averaged from twenty-four healthy persons, the limits being five and eight minutes. The normal average for blood from the ear was three minutes, with two- and four-minute limits, thus showing that blood obtained by skin puncture and contaminated by tissue-juice clots twice as rapidly in the normal individual as blood taken directly from the vascular system.

Accelerated Coagulation Time. Acceleration of the coagulation time (three and one-half minutes or less) was found in some cases, notably in 5 patients with typhoid fever, 4 of whom developed thrombosis. There were a number of isolated cases which showed a hastened coagulation time, including 1 of the 3 cases of myelogenous leukemia, 1 of the cases of diabetes, 1 case of typhus fever, and 1 of endocarditis.

Delayed Coagulation Time. Of the 125 cases, delay of the coagulation time occurred in 47, which may be divided into three main groups—blood diseases, jaundice, and acute infections.

Blood Diseases. Two cases of hemophilia had markedly prolonged clotting time, the longest in the series, almost an hour; both had hemorrhages. One case of purpura hæmorrhagica had delayed coagulation time, the first result being ten minutes; two and one-half weeks later the test gave fifteen minutes (the patient had grown worse steadily and died a week after the second test).

Cases of primary pernicious anemia varied considerably in coagulation time, although the average time (ten minutes) was longer than normal. Those cases that were the sickest had the most delayed coagulation time, and two cases with a coagulation time of fifteen minutes died.

One case of splenic anemia, a fatal case of acute lymphatic leukemia, and one case of myelogenous leukemia without hemorrhage showed delayed coagulation times (ten to fifteen minutes). Two cases of myelogenous leukemia were not delayed.

Liver Diseases and Jaundice. Jaundice and liver cases varied considerably in coagulation time, those with only slight jaundice being practically normal, while those with marked jaundice were often delayed. One striking case with gallstones and complete jaundice had a coagulation time of fifteen and one-half minutes, and died of secondary hemorrhage soon after operation. Another clinically similar case of gallstones, with complete jaundice, had a coagulation time of eight minutes before operation, and had no hemorrhage. Cases of syphilis and atrophic cirrhosis of liver with jaundice were above normal limits, while similar cases without jaundice were normal. Cancer of the liver even with jaundice did not retard the coagulation time in four cases. Hanot's cirrhosis of the family type, with slight to moderate jaundice, showed in two cases a marked delay in coagulation time, twelve to seventeen minutes. Both cases (sisters) had hemorrhage. One died of spontaneous hemorrhage from mucous membranes in spite of transfusion.

Acute Infections. Of acute infectious diseases, lobar pneumonia gave the most prolonged coagulation time (average fifteen and one-half minutes). One of the six cases that was very sick had blood which took thirty-five minutes to clot. One mild case was normal (six and one-half minutes). In convalescence from pneumonia the coagulation time approaches the normal again as shown by several of our cases, especially a very severe one with a delayed time of thirty-five minutes, which became six minutes several days after crisis. This return to normal after retardation in pneumonia has been well shown by Dochez.[17]

Of the 16 cases of typhoid, 7 had delayed coagulation time (eight to fifteen minutes); 2 of the 7 had hemorrhages, 1 dying; 4 cases were normal, and the other 5 hastened; 4 of the latter had thrombosis, as we have noted above. Dr. Oscar Richardson in an unpublished study at the Massachusetts General Hospital found that blood taken from the heart of typhoid fever patients at autopsy varied enormously in the coagulation time. In general, the cases with hemorrhage gave a prolonged coagulation time, and the cases with thrombosis an accelerated coagulation time.

One of the typhoid cases with definitely prolonged coagulation time in the acute stage of illness became normal in convalescence (thirteen minutes to seven minutes), another dropped from nine minutes to seven minutes.

Other septicemias besides pneumonia and typhoid tend to show abnormality in coagulation time. Staphylococcus aureus and streptococcic septicemia seem to delay clotting, as found in two cases (thirteen minutes and eleven and one-half minutes respectively).

Other mild acute infections showed little change in coagulation time. Three cases of acute endocarditis, one dying soon after, gave times rather shorter than normal.

Cardiac and gastric cases studied were normal. Severe nephritis gave in one case a definitely prolonged coagulation time (fourteen minutes), and in another, a fatal case, with marked edema, a coagulation time of eight minutes.

Hemoptysis in tuberculosis in two cases was not accompanied by prolonged coagulation time.

Menstruation in 3 cases did not prolong the coagulation time. In 1 case with nose bleed the coagulation time was delayed during menstruation; 250 cases tested by Keller[18] during, before, and after menstruation showed no change in coagulation time. Pregnancy and menopause he also found did not effect the coagulation time.

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[17] Loc. cit.

[18] Arch. f. Gyn., Part 3, xcvii, 540.

In general, the coagulation time corresponded closely to the clinical picture of hemorrhage. The test was of distinct prognostic value in cases of jaundice undergoing operation. In pernicious anemia and certain other blood diseases a further delay in coagulation time was synchronous, with aggravation of symptoms. In the acute infections, excluding typhoid, the more severe infections seemed to be associated with a more delayed coagulation time. In typhoid fever there seemed to be a distinct parallelism between thrombosis and hemorrhage and the coagulation time. This question must be subjected to further study.

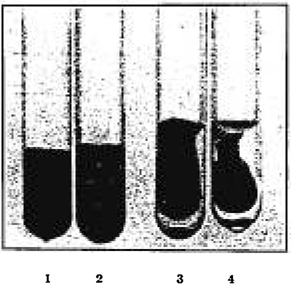

FIG. 2.—1, normal clot before retraction; 2, hemophiliac clot before retraction; 3, normal clot after retraction; 4, hemophiliac clot after retraction.

The study of the nature and retraction of the clot has been interesting. There have been 35 cases out of the 125 which we have tested in which there has been more or less settling of the red blood corpuscles. Of these, 31 have had definitely long coagulation times and 3 others on the border-line of normal. The most marked settling of corpuscles occurred in 6 cases, in which the coagulation time was twice normal or more. In 1 case (a patient with hemophilia) the corpuscles settled so much before coagulation that they made up but one-quarter of the bulk of the blood. In this case the coagulation time was more than eight times normal. In another case of hemophilia the corpuscles settled to about one-half the bulk, as shown in the accompanying illustration (Fig. 2).

The colorless clot above the corpuscles is evidently produced by the differences in specific gravity of the blood elements, and is the so-called "buffy-coat" described by Davy[19] and Dalton[20] in the first half of the last century. There were 47 cases with delayed coagulation time. Only 12 showed no settling of the corpuscles, and they were no longer than ten minutes at the most. A few of the 12 gave a clot of flimsy texture. As a rule therefore the delay in coagulation time goes hand-in-hand with the settling of the corpuscles and "buffycoat," and the two may almost be used as a check on each other. If either one or other is present the blood tested is not normal, but the usual combination of the two is conclusive.

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[19] Researches, 1839, ii, 46.

[20] Treatise on Human Physiology, 1859, p. 195.

Retraction of the Clot. There were but three cases in which no retraction of the clot took place. These were a fatal case of purpura hæmorrhagica, tested twice, a case of pernicious anemia, and a fatal case of jaundice and cholemia of unknown etiology.

Relation of the Coagulation Time to the Retraction of the Clot. The coagulation time in these three cases was twelve and one-half minutes, thirteen and one-half minutes, and seven minutes respectively. The various other cases with a delayed coagulation time showed a normal retraction of the clot, consequently the retraction of the clot did not seem to depend upon the mere delay in the coagulation time.

Relation of the Number of Blood Platelets to the Retraction of the Clot and to the Coagulation Time. The blood platelets were almost entirely absent in the case of purpura hæmorrhagica, as has already been pointed out by Denys,[21] Hayem,[22] and Duke.[23] The blood platelet count in the case of pernicious anemia was 1000. There was no examination of the blood platelets in the third case. Other cases with considerably decreased platelet counts showed fairly consistently delay in clot retraction. On the other hand, one case of hemophilia had a blood platelet count of 200,000, and retraction was normal. The problem of the relation of the blood platelets to the retraction of the clot is now being studied further, but in general these cases tend to suggest that the blood platelets have more to do with the retraction of the clot than with its actual formation, as has already been pointed out by Duke.[24]

The color abnormalities observed have been chiefly three: The lighter color of the blood in severe anemias, the chocolate-brown color in leukemia, and the definitely yellow serum expressed from the retracting clot in cases of jaundice and pernicious anemia.

SUMMARY. A simple method of determining the coagulation time of blood has been studied. It obviates the contact of blood with tissue juice which introduces a larger element of error. The method seems reliable in ordinary room temperatures. In cases tested the tendency to bleed corresponded closely to the coagulation time.

[21] La Cellule, 1887, vol. iii; 1889, v, 189.

[22] Presse Méd., 1895, p. 233.

[23] Arch. Int. Med., November 15, 1912.

[24] Loc. cit.